A Three-step Synthesis of a Gliotoxin Analogue with Anti-reverse Transcriptase Activity

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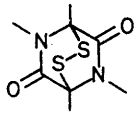
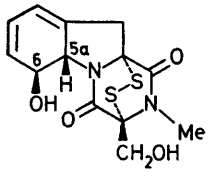
Summary A practical, 3-step synthesis of general applicability to analogues of gliotoxin has been devised and used to prepare the potent antiviral compound (**12**) in 37% yield.

THE epidithiodioxopiperazine ring system (**1**), common to a number of fungal metabolites, appears to be the site of the potent antiviral, antibacterial, or antifungal activities of this group.[1,2] Several syntheses of simple derivatives of (**1**) have appeared[3] and Kishi and his co-workers have recently reported[4] a 12-step synthesis of (±)-dehydrogliotoxin, *i.e.* the 5a—6 dehydro racemate of gliotoxin (**2**). We report a much simpler route to analogues of gliotoxin which features the reaction of α-keto acyl chlorides with indolenine-2-carboxamides.



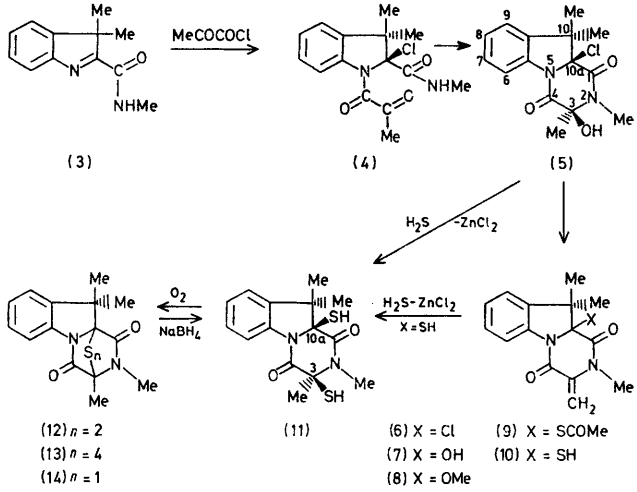
(1)



(2)

Pyruvoyl chloride[5] and the carboxamide† (**3**) in CCl_4 reacted within 50 min at room temperature to form the Leuchs' adduct[6] (**4**) [δ‡7·89 (m, 6-H) and 3·19 (d, NMe)]. 80 min after mixing, this intermediate had been converted completely into (**5**),[7] which appeared to be one stereoisomer[8] by ^{1}H n.m.r. spectroscopy [δ 8·31 (m, 6-H) and 3·47 (s, NMe)]. When stirred for 16 h, (**5**) is transformed into a mixture of (**6**) [δ 6·37 (d, C=C–H_A) and 5·52 (d, C=C–H_B)] and (**7**), the latter apparently arising from the water produced on spontaneous dehydration. The chloroalkene (**6**) could be converted quantitatively into (**7**) with 1 equiv. of NaOH in MeOH, while treatment with MeOH–CCl_4 or thioacetic acid and BF_3,Et_2O in CH_2Cl_2 gave (**8**) (60%) and (**9**) (88%), respectively.

When H_2S was bubbled through a CH_2Cl_2 solution of (**6**) for 1 h at room temperature, the mercaptoalkene (**10**) [δ 4·75 (br s, SH)] resulted. In addition a 1:1 mixture of (**6**) and (**7**) was quantitatively converted into (**10**) within 2 h with H_2S–$ZnCl_2$ at 0 °C. When (**5**) or (**10**) were exposed to these conditions for 8 h, the *cis*-dithiol (**11**) [δ 4·24 and 3·44 (s, 2 × SH) and 2·43 (s, 3-Me)] resulted, probably indicating the intermediacy of (**10**), since (**5**) is so easily dehydrated.



(3) (4) (5)

(12) n = 2
(13) n = 4
(14) n = 1

(11)

(6) X = Cl
(7) X = OH
(8) X = OMe

(9) X = SCOMe
(10) X = SH

The unexpected *cis*-orientation of the C(3) and C(10a) thiol groups is proved by the ready oxidation (O_2, MeOH–H_2O) of the dithiol (**11**) to the disulphide (**12**) [37% yield from (**3**), m.p. 136—138 °C; δ 8·40 (m, 6-H), 7·64 (m, 7—9-H), 3·50 (s, NMe), 2·48 (s, 3-Me), and 2·18 and 1·98, (s, 10-αMe and 10-βMe); mass spectrum (chemical ionization, NH_3): *m/e*, 338 (M+NH_4, 33%), 321 (M+H^+, 100%), and 257 (M+H^+–S_2, 71%)] and by the conversion (58%) of (**11**) into the epitetrathiodioxopiperazine (**13**)§ with S_2Cl_2 in dry $CHCl_3$. The disulphide (**12**) could be converted into the dithiol (**11**) by treatment with $NaBH_4$ in EtOH, while reaction with excess of PPh_3 in EtOH[9] gave the mono-sulphide (**14**) [δ 7·82 (m, 6-H), 3·29 (s, NMe), and 2·17 (s, 3-Me)] in 20% yield.

Compound (**12**) inhibited reverse transcriptase,[10] the

† Prepared in 90% yield from ethyl 3,3-dimethylindolenine-2-carboxylate[6c] and methylamine in dry monoglyme at 80 °C in an autoclave; m.p. 109—110 °C (from MeOH–hexane).

‡ ^{1}H N.m.r. spectra expressed in δ values were measured using external hexamethyldisiloxane, for solutions in either CCl_4 (**4**)—(**7**) or $CDCl_3$ (**10**)—(**14**). Only essentials are given.

§ Chemical ionization mass spectrum (NH_3): *m/e* 402 (M+NH_4^+, 48%), 385 (M+H^+, 83%), 370 (M+NH_4^+ − S, 32%), 353 (M+H^+ − S, 43%), 338 (M+NH_4^+ − S_2, 22%), 321 (M+H^+ − S_2, 32%), 289 (M+H^+ − S_3, 5%), and 257 (M+H^+ − S_4, 100%).

RNA-dependant DNA polymerases of RNA tumour viruses, at concentrations of $3{\cdot}9 \times 10^{-4}$M (130 μg/ml) and $3{\cdot}9 \times 10^{-5}$M (13 μg/ml) where the poly A-dependent incorporation of ^{3}H-dTMP residues with enzyme derived from Rauscher leukeamia virus was 14 and 41%, respectively, of the blank activity.[11]

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[1] For a review, see A. Taylor in 'Microbial Toxins,' Vol. VII, Eds. S. Kadis, A. Ciegler, and S. J. Ajl, Academic Press, New York, 1971, p. 337.

[2] A. Kato, T. Saeki, S. Suzuki, K. Ando, G. Tamura, and K. Arima, *J. Antibiotics*, 1969, **22**, 322; A. D. Argoudelis, and F. Reusser, *ibid.*, 1971, **24**, 383; K. H. Michael, M. O. Chaney, N. D. Jones, M. M. Hoehn, and R. Nagarajan, *ibid.*, 1974, **27**, 57; R. L. DeVault and W. Rosenbrook, Jr., *ibid.*, 1973, **26**, 532; G. M. Strunz, M. Kakushima, M. A. Stillwell, and C. J. Heissner, *J.C.S. Perkin I*, 1973, 2600.

[3] P. W. Trown, *Biochem. Biophys. Res. Comm.*, 1968, **33**, 402; H. Poisel and U. Schmidt, *Chem. Ber.*, 1971, **104**, 1714; E. Oehler, H. Poisel, F. Tateruch, and U. Schmidt, *ibid.*, 1972, **105**, 635; T. Hino and T. Sato, *Chem. Pharm. Bull.* (*Japan*), 1974, **22**, 2866; S. G. Svokos and R. B. Angier, Ger. P. 2,029,306 (*Chem. Abs.*, 1971, **74**, 53845); J. Yoshimura, H. Nakamura, K. Matsunari, and Y. Sugiyama, *Chem. Letters*, 1974, 559; G. M. Strunz and M. Kukushima, *Experientia*, 1974, **30**, 719; Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, 1973, **95**, 6490; P. J. Machin and P. G. Sammes, *J.C.S. Perkin I*, 1974, 698.

[4] Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Amer. Chem. Soc.*, 1973, **95**, 6492.

[5] H. C. J. Ottenheijm and J. H. M. de Man, *Synthesis*, 1975, 163.

[6] The reaction of acyl chlorides with indolenines is a general one discovered by Leuchs and his co-workers: H. Leuchs, A. Heller, and A. Hoffmann, *Ber*, 1929, **62**, 871, and employed in an earlier synthesis of indole-2-thioethers: T. Wieland and D. Grimm, *Chem. Ber.*, 1965, **98**, 1727; and an earlier approach to anhydrogliotoxin analogues: H. C. J. Ottenheijm, T. F. Spande, and B. Witkop, *J. Amer. Chem. Soc.*, 1973, **95**, 1989.

[7] The reaction of primary or secondary amides with the α-carbonyl group of pyruvoyl derivatives is a general one (*cf.* R. B. Herbst, *J. Amer. Chem. Soc.*, 1939, **61**, 483) and has seen recent application in the synthesis of α-mercapto-α-amino carboxylic acid derivatives (H. C. J. Ottenheijm, A. D. Potman, and T. van Vroonhoven, *Rec. trav. Chim.*, 1975, **94**, 135).

[8] This stereoselectivity accords with recent observations in a similar reaction: J. Häusler and U. Schmidt, *Chem. Ber.*, 1974, **107**, 2804.

[9] S. Safe and A. Taylor, *J. Chem. Soc.* (*C*), 1971, 1189.

[10] These tests were kindly performed by Dr. H. P. J. Bloemers, Department of Biochemistry, University of Nijmegen, The Netherlands. The methods used are described in H. P. J. Bloemers and A. van der Horst, *FEBS Letters*, 1975, **52**, 141.

[11] This activity is of the same order of magnitude as that for gliotoxin. The latter inhibited endogenous reverse transcriptase activity of Rauscher Sarcoma Virus: with 50 μg/ml, 25% of the enzyme activity remained; personal communication, S. Mizutani and H. M. Temin, McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, Wisconsin.